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(57) Abstract

The present invention relates to intravascular stents, stent assemblies, methods of manufacturing intravascular stents and uses thereof. The intravascular stents of the present invention comprise copper which leads to the generation of sufficient nitric oxide *in vivo* to substantially prevent platelet activation.

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STENT CONTAINING COPPER

The present invention relates to intravascular stents, stent assemblies, methods of manufacturing intravascular stents and uses thereof.

Intravascular stents are increasingly being used to maintain patency and to prevent restenosis of blood vessels occluded by, for example, atheromatous arterial disease. Restenosis is the closure of a blood vessel, particularly an artery, following trauma to the vessel caused by efforts to open an occluded portion of a vessel, by for example, dilation, ablation, atherectomy or laser treatment. A particular use of stents is to prevent restenosis in the coronary circulation following transcutaneous balloon angioplasty. Stents may also be used to repair aneurysms.

In order to prevent restenosis, a stent is inserted into the relevant vessel, generally by a catheter, and expanded so that the stent makes contact with the walls of the affected vessel.

However, a problem with the use of conventional stents is their propensity to cause local blood coagulation and thrombosis formation leading to subsequent occlusion of the stented vessel.

Currently, in order to overcome this problem, patients receiving stents are given systemic therapy using anticoagulants such as heparin and warfarin, and antiplatelet agents such as aspirin. However, the use of systemic therapy in combination with stents can lead to bleeding complications, which may on occasion be severe (see Wong and Leon, (1995), Current Opinions in Cardiology, 10, pp 404-411).

It has also been proposed in the prior art that stents are seeded with endothelial cells (see Dichek *et al.*, (1989), Circulation, 80, pp 1347-1353). Dichek *et al.* describe the seeding of endothelial cells onto stainless steel stents until the stents are fully covered. The cells on the stents are then able to be delivered to the vascular wall where they can provide therapeutic proteins. Other methods for providing therapeutic substances to vascular walls by means of stents have also been proposed in, for example, published International Patent

Applications WO 91/12779 and WO 90/13332. In these applications it is suggested that antiplatelet agents, anticoagulant agents, antimicrobial agents, antimetabolic agents and other drugs could be supplied in stents to reduce the incidence of restenosis.

In EP-A-0 566 245, a stent is described comprising fibrin which is said to reduce the incidence of restenosis at the site of vascular injury.

In EP-A-0 623 354, a stent is described which has a polymer formed thereon in which a therapeutic substance is dispersed.

Other stents are described elsewhere with other various coatings. For example, in EP-0 627 226, stents are described coated with biocompatible polymeric material.

However, none of the prior art stents efficiently prevent restenosis occurring following vascular injury, such as that following transcutaneous balloon angioplasty, and the prior art stents generally require the need for the use of systemic drugs in order to avoid local blood coagulation and thrombosis formation leading to subsequent occlusion. There remains therefore a need for improved stents capable of resisting and preventing restenosis.

According to the present invention there is provided an intravascular stent comprising copper.

The present invention overcomes a number of problems associated with prior art stents and provides an efficient method to prevent the re-occlusion of stented vessels and eliminates or reduces the need for the use of systemic anticoagulant and antiplatelet agents.

It is believed that the presence of copper on the surface of the stent leads to increased levels of nitric oxide in the vicinity of the stent.

Nitric oxide is normally generated by endothelial cells which line all blood vessels and is thought to be important in preventing platelet activation in healthy vessels. Nitric oxide is also generated by nitrosothiol compounds such as S-nitrosoglutathione (GSNO) which have been detected circulating in the bloodstream. For GSNO to breakdown

chemically and form nitric oxide, it has been reported that copper (I) ions must be present (see Gordge *et al.*, (1995), British Journal of Pharmacology, 114, pp 1083-1089). It is believed that copper (I) ions are present in trace amounts in the circulation and intravascular tissue leading to the innate generation of nitric oxide.

Without prejudice to the present invention it is believed that copper present in the stent, when exposed to an aqueous solution such as blood plasma, produces copper (I) ions on its surface which enhance the formation of nitric oxide from nitrosothiol compounds in the vicinity of the stent, thereby preventing or reducing platelet activation.

Preferably, the stent of the present invention comprises copper on an exposed surface.

Any design of stent can be used in the present invention, including the self-expanding type or the balloon-expandable type. Examples of stent designs useful in the present invention are described in US-A-4 733 665, US-A-4 800 882 and US-A-4 886 062. The stent can be made of virtually any material provided the material is biocompatible and has physical properties suitable for its function. The stent may be made from metal such as stainless steel or titanium, biostable polymers such as polyurethanes, silicones and polyesters, or bioabsorbable polymers such as poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly(ethylene oxide)/poly(butylene terephthalate) copolymers. Preferably, the stent is formed from stainless steel.

The term "copper" is used to describe metallic copper or any compound (such as copper containing chelate or protein, e.g. copper, zinc superoxide dismutase) or alloy comprising copper (such as a copper-steel alloy) which when exposed to an aqueous solution is capable of forming copper (I) ions. Preferably, the stent of the present invention comprises metallic copper on an exposed surface.

The term "an exposed surface" is used herein to describe a surface of the stent which when inserted into the lumen of a vessel and expanded, is in contact with an aqueous fluid such as blood plasma.

The copper on the exposed surface of the stent of the present invention in use, will come into contact with an aqueous fluid and copper (I) ions will be formed. The copper (I) ions allow GSNO to break down and form nitric oxide. The nitric oxide formed will prevent platelet activation and thereby prevent platelet aggregation and thus reduce the tendency of clot formation on the stent surface and in the regions adjacent the stent.

The stent of the present invention will therefore be useful in reducing restenosis of the diseased vessel and will reduce the need for the use of systemic anticoagulant and antiplatelet agents.

Copper may be provided in a form suitable for incorporation in the material of construction of the stent. For example the stent may be constructed of a copper alloy (such as a copper-steel alloy). Alternatively, the copper may be provided in a form suitable for attaching to the stent or as a coating on the stent. For example, the copper may be provided as a metal, alloy or copper containing protein for coating the stent. In a preferred embodiment, the stent of the present invention has a coating of copper.

The copper coating may be applied to the stent using any conventional coating technique, such as plating or painting. Preferably, where the stent is formed from metal, a metallic copper coating is applied using electroplating techniques well known to those skilled in the art. Such techniques are described in Practical Electroplating Handbook, N.V. Parthasaradhy, 1989.

The coating may cover all or part of the stent. Preferably, the stent of the present invention has an external surface which in use, contacts the wall of a vessel, and an internal surface which defines the lumen of the stent. Preferably, copper is provided on at least a part of the internal surface of the stent.

The copper coating formed on the stent of the present invention may be thin, preferably 0.01 to 100 μm, more preferably 0.1 to 10 μm thick.

In a particular preferred embodiment, the stent of the present invention is made from stainless steel and at least a part of the exposed surface has a copper coating formed thereon.

In a preferred embodiment, the stent of the present invention comprises sufficient copper on an exposed surface to lead to the generation of sufficient nitric oxide *in vivo*, to substantially prevent platelet activation in the regions adjacent the stent.

In a further preferred embodiment, the stent of the present invention further comprises a therapeutic substance. Preferred therapeutic substances are described in WO 91/12779 and WO 90/13332, and include antiplatelet agents, anticoagulant reagents, antimicrobial agents and antimetabolic agents.

Therapeutic substances may be incorporated into the stent of the present invention using the methods described in EP-A-0 566 245, wherein said therapeutic substances are incorporated into the stent in the form of microcapsules, or in EP-A-0 623 354, wherein therapeutic substances are incorporated into the stent by applying a solution which comprises a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent.

In another preferred embodiment, the stent of the present invention may further comprise a biocompatible coating, which may be present on either or both the internal or external stent surfaces. In particular, the copper may be covered with a biocompatible coating such as a membrane which is porous to platelets and GSNO but reduces direct contact of copper with the arterial wall, which may cause inflammation of the arterial wall. Suitable membrane materials include phosphoryl choline (Biocompatible Limited, Farnham Surrey). Methods for applying biocompatible coatings are described, for example, in EP-A-0 627 226.

In a further preferred embodiment, the stent of the present invention further comprises a nitrosothiol compound such as GSNO.

In a second aspect of the present invention there is provided a stent assembly comprising the stent of the present invention and a catheter. Preferably, the stent assembly additionally comprises a balloon.

The stent assembly is used to insert the assembly into the lumen of a vessel. When the stent is a balloon inflatable stent the catheter has the balloon attached at a distal end, and the stent is mounted around the balloon. The stent is delivered to the desired site by the catheter using conventional percutaneoneous techniques well known to those skilled in the art. The balloon is then used to expand the stent so that it makes contact with the walls of the vessel, and the catheter and balloon are then withdrawn leaving the stent in place.

In a third aspect of the present invention there is provided a method for making the stent of the present invention comprising attaching copper to an exposed surface of a stent. The copper may be attached using mechanical techniques such as welding, stapling or gluing. Preferably, the copper is attached to an exposed surface of a stent by electroplate techniques. Electroplate techniques are well known to those skilled in the art and such techniques are described in Practical Electroplating Handbook, N.V. Parthasaradhy, 1989.

A fourth aspect of the present invention is the stent of the present invention for use in therapy.

The present invention further provides a method of preventing or reducing restenosis comprising the use of a stent according to the present invention.

It is particularly preferred that the stent of the present invention is used in conjunction with a composition comprising a nitrosothiol compound such as GSNO. The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile

aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. The administration of the composition comprising the nitrosothiol compound will lead to a higher level of the nitrosothiol compound in the body and in turn will lead to a higher level of nitric oxide in the vicinity of the stent, thereby preventing or reducing restenosis.

In a fifth aspect of the present invention there is provided a kit for use in the treatment of restenosis comprising the stent of the present invention and a composition comprising a nitrosothiol compound suitable for administration to a patient.

Preferably, the composition is in a form suitable for oral or intravenous administration.

In a sixth aspect of the present invention there is provided a kit for use in the treatment of restenosis comprising the stent of the present invention and a catheter.

Preferably, the kit additionally comprises a balloon.

A seventh aspect of the present invention is the use of copper in the manufacture of the stent of the present invention for use in the treatment of restenosis.

The present invention is now described, by way of example only, with reference to the accompanying Figures, in which:

Figure 1 shows the effect of copper metal and copper-containing alloys on nitric oxide generation from 10 μM GSNO;

Figure 2 shows the effect of different surface areas of copper on nitric oxide (NO) release from 10μM GSNO; and

Figure 3 shows the effect of the combination of 1μM GSNO and copper metal on ex-vivo platelet aggregation (*=$p<0.05$).

Effect of Copper Metal and Copper Alloys on Nitric Oxide formation from S-Nitrosoglutathione

Nitric oxide (NO) was generated by adding 200 µL samples of 10µM S-nitrosogluthathione (GSNO) to a reaction flask containing distilled water and different surface areas of copper or copper alloys. The alloys used were Numetal™ (Goodfellow, Cambridge), containing 5% copper and nickel silver, containing 62% copper. The NO generated was detected by a Sievers NOA™ 280 analyzer using a chemiluminescence method. Results shown in Figure 1 suggest that the ability of the metal to generate NO from GSNO is related to the amount of copper present.

Stainless steel (316L alloy) from which most commercially available stents are manufactured does not generate significant amounts of NO from GSNO (data not shown).

Figure 2 shows that by increasing the surface area of copper, the rate of NO production is increased, up to a maximum level.

Effect of Metallic Copper on Platelet Aggregation with S-Nitrosoglutathione

In this experiment, venous blood was collected from fourteen healthy volunteers who were not on drug therapy. Venous blood samples were added to tubes containing 13mM trisodium citrate. Platelet rich plasma was prepared by centrifugation at 150g for 12 minutes at 25°C. Collagen-induced platelet aggregation was measured in 0.5ml aliquots following addition of 1µm GSNO and/or copper metal (added as wire with surface area 2 mm^2). Whereas the concentration of GSNO alone had no effect on platelet aggregation, the addition of copper caused an impairment of aggregation. See Figure 3.

Manufacture of a Copper Coated Stent

A stainless steel balloon-expandable stent was electroplated with copper over its entire surface using the cyanide bath method. The cyanide bath method is described in

Practical Electroplating Handbook, N.V. Parthasaradhy, 1989. However, any conventional method for copper plating stainless steel may be used.

The copper coated stent may be used in standard intravascular stent treatments.

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Claims

1. An intravascular stent comprising copper.

2. A stent according to claim 1 comprising copper on an exposed surface.

3. A stent according to claim 1 or 2 which has an external surface which in use contacts the walls of a vessel and an internal surface which defines the lumen of the stent, wherein the copper is on at least a part of the internal surface of the stent.

4. A stent according to any one of claims 1 to 3 having a coating of copper.

5. A stent according to claim 4, wherein the copper coating is 0.01 to 100 μm thick.

6. A stent according to claim 4 or 5, wherein the stent is made from stainless steel and at least part of the exposed surface has a copper coating.

7. A stent according to any preceding claim wherein the copper is present as copper metal.

8. A stent according to any lone of claims 1 to 6 wherein the copper is present as a copper alloy.

9. A stent according to any one of claims 1 to 6 wherein the copper is present as a copper-containing protein.

10. A stent according to any one of the preceding claims, wherein the stent comprises sufficient copper to lead to the generation of sufficient nitric oxide in vivo to substantially prevent platelet activation in the regions adjacent the stent.

11. A stent according to any one of the preceding claims wherein the stent further comprises a biocompatible coating.

12. A stent according to any one of the preceding claims further comprising a therapeutic substance.

13. A stent according to claim 12, wherein the therapeutic substance is an anticoagulant agent, an antiplatelet agent, an antimetabolic agent or an antimetabolic agent.

14. A stent according to any one of the preceding claims further comprising a nitrosothiol compound.

15. A stent assembly comprising the stent according to any one of the preceding claims and a catheter.

16. A stent assembly according to claim 15 which additionally comprises a balloon.

17. A method for making the stent according to any one of claims 1 to 14, comprising attaching copper to an exposed surface of a stent.

18. A method according to claim 17 wherein copper metal is attached to the exposed surface of a stent by electroplating.

19. A stent according to any one of claims 1 to 14 for use in therapy.

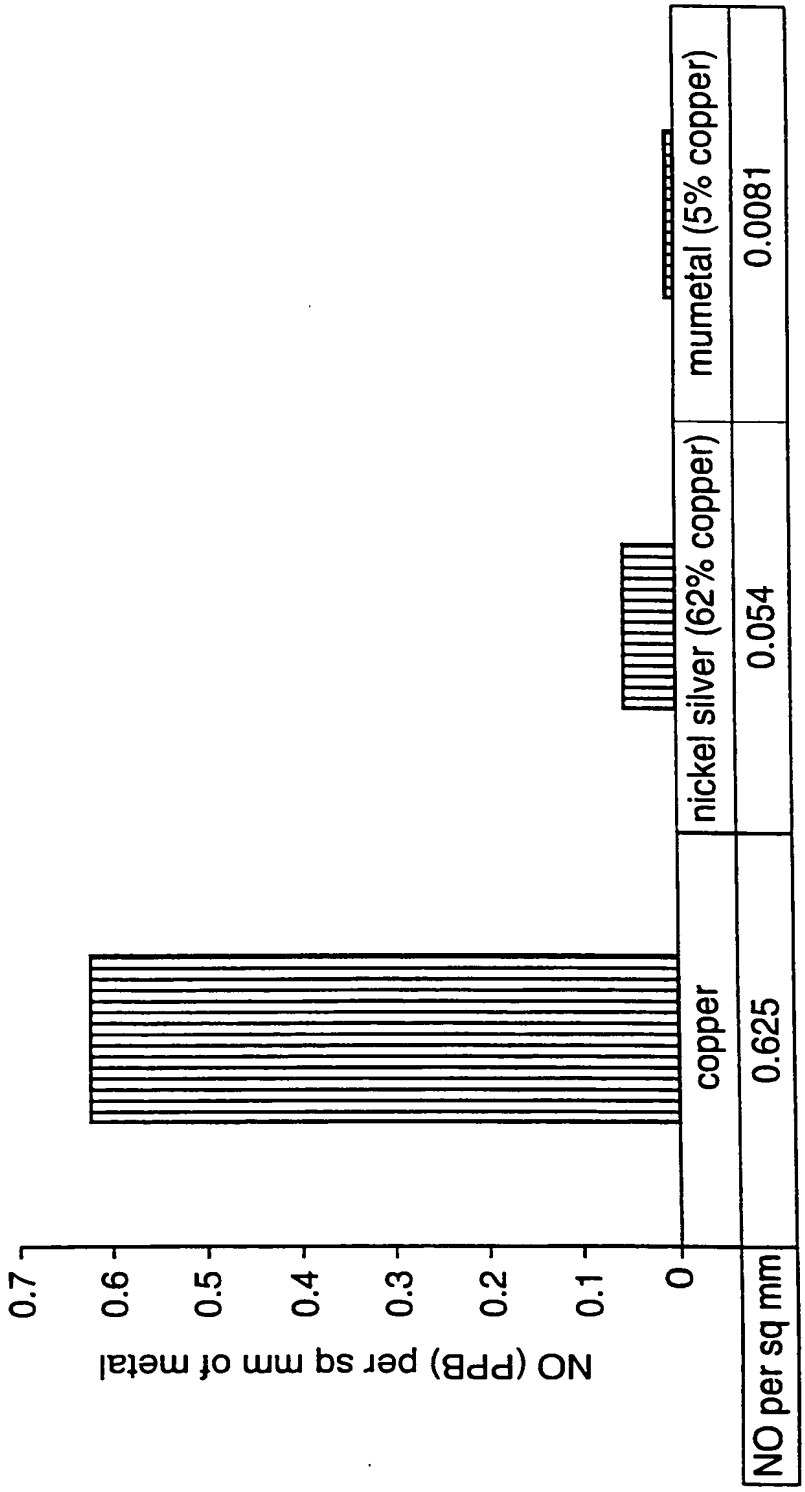
20. A kit for use in the treatment of restenosis comprising the stent of any one of claims 1 to 14 and a composition comprising a nitrosothiol compound suitable for administration to a patient.

21. A kit according to claim 20 wherein the composition comprising a nitrosothiol compound is suitable for oral or intravenous administration.

22. A kit for use in the treatment of restenosis comprising a stent assembly according to claim 15 or 16.

23. The use of copper in the manufacture of a stent according to any one of claims 1 to 14 for use in the treatment of restenosis.

FIG. 1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0.6
0.5
0.4
0.3
0.2
0.1
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mumetal (5% copper)
NO per sq mm
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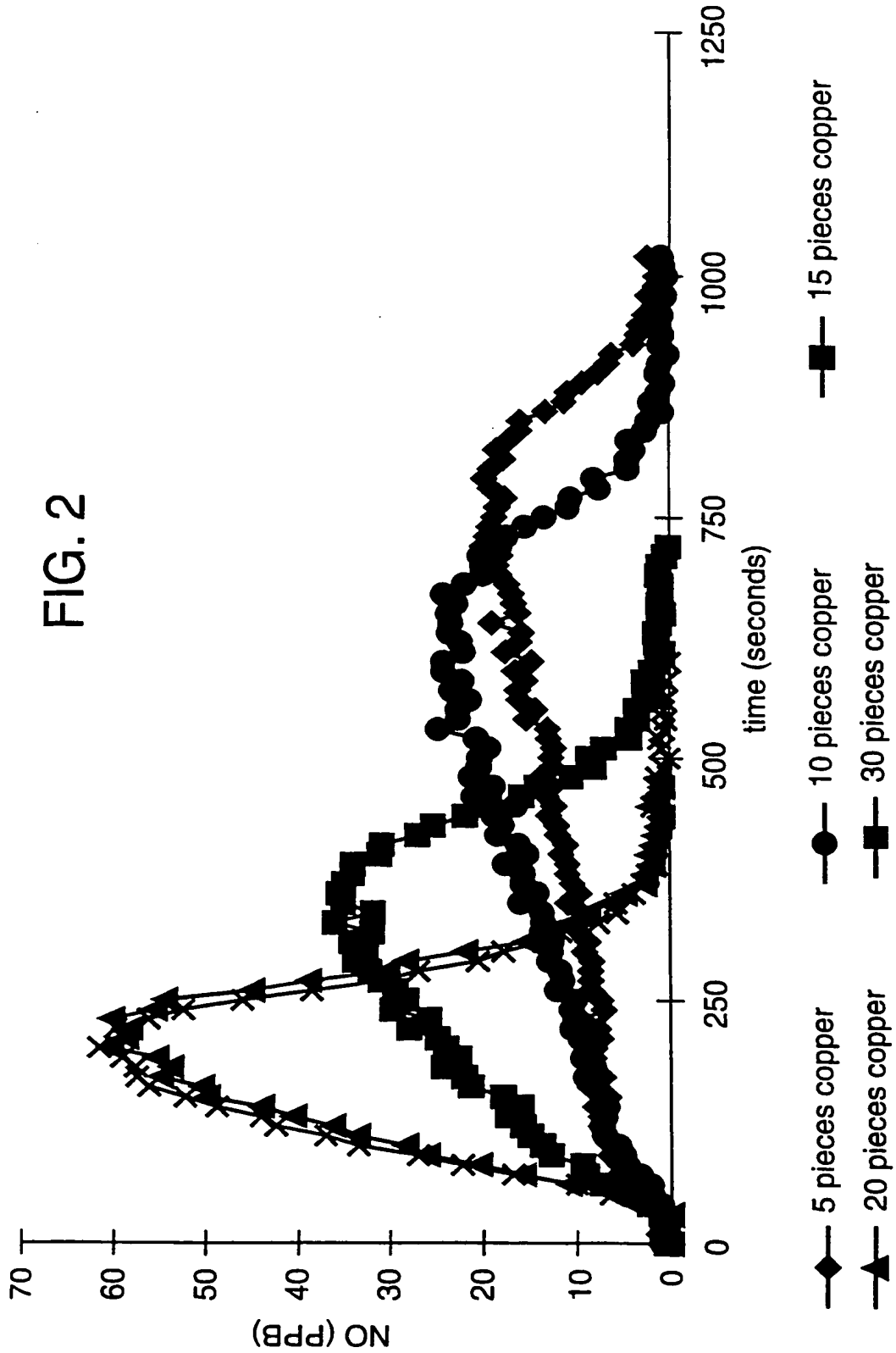
0.054
0.0081

FIG. 2


NO (PPB)
0
10
20
30
40
50
60
70
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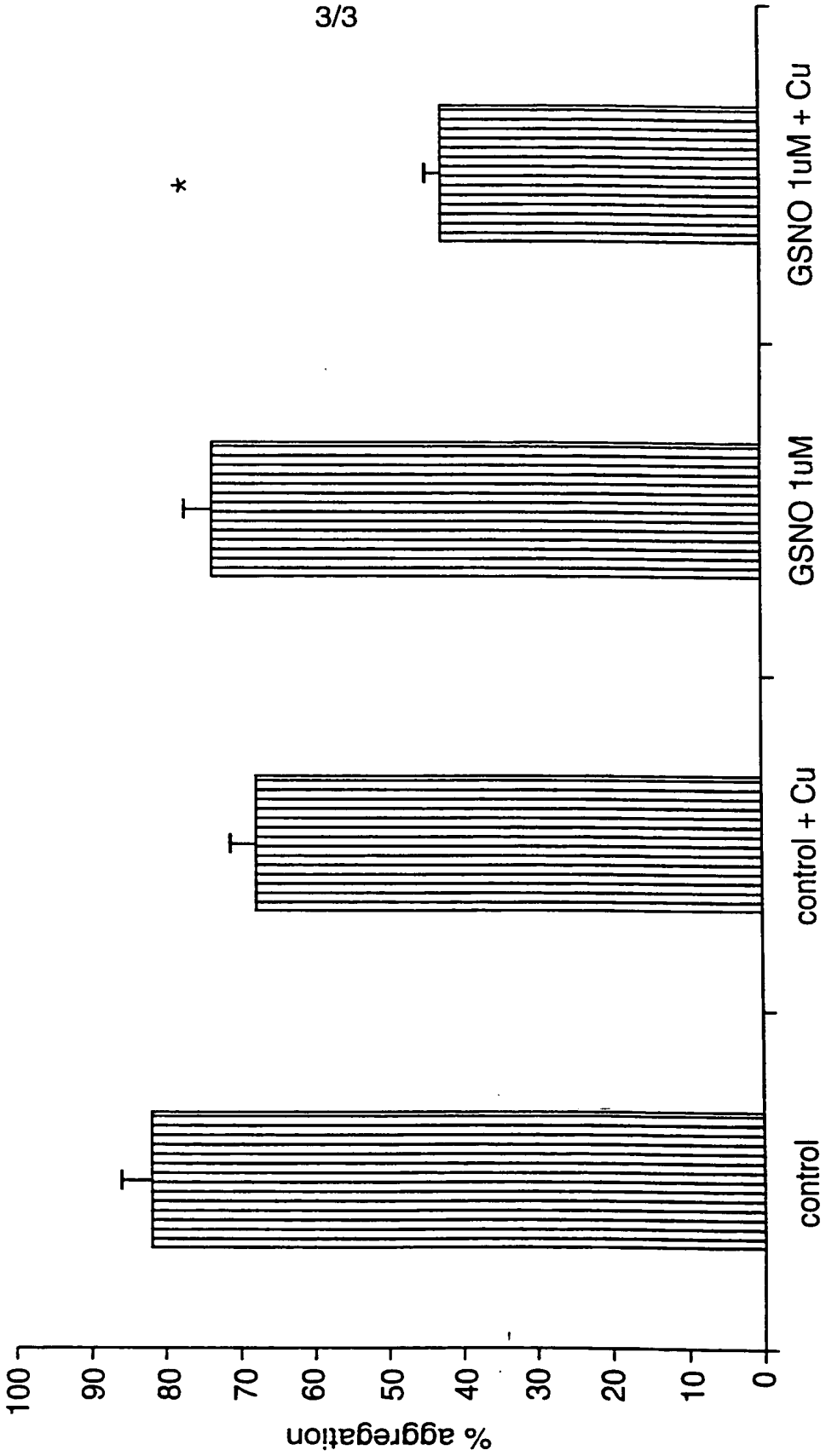
250
500
750
1000
1250
time (seconds)
5 pieces copper
10 pieces copper
15 pieces copper
20 pieces copper
30 pieces copper

FIG. 3


% aggregation
100
90
80
70
60
50
40
30
20
10
0
*
control
control + Cu
GSNO 1uM
GSNO 1uM + Cu

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/02238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/06 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F C07D A61K C07K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 20928 A (QUANAM MEDICAL CORP) 22 May 1998 (1998-05-22)	1-3,8, 11-13, 15,16, 19,22,23
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Y	US 5 536 723 A (LOSCALZO JOSEPH ET AL) 16 July 1996 (1996-07-16) column 16, line 40 - column 17, line 12 column 25, line 3 - line 27 claim 2 ---	14,20,21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 September 1999	15/09/1999

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International Application No
PCT/GB 99/02238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
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